Reversal of cardiopulmonary exercise intolerance in patients with post-thrombotic obstruction of the inferior vena cava

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Abstract: BACKGROUND It is unclear whether cardiopulmonary exercise intolerance in patients with chronic obstruction of the inferior vena cava (IVC) is reversible following endovascular IVC reconstruction. METHODS In 17 patients (mean age 45 ± 15 years, 71% men) with post-thrombotic syndrome due to IVC obstruction and preserved left ventricular ejection fraction (mean 58 ± 3%), we performed cardiopulmonary exercise testing before and 3 months after IVC reconstruction (mean 4.1 ± 1.5 implanted stents). The median time from latest episode of deep vein thrombosis to intervention was 150 (interquartile range 102-820) days. RESULTS At baseline, 12 (71%) patients reported New York Heart Association (NYHA) class II or III symptoms, 76% did not achieve >85% of predicted oxygen uptake at peak exercise (mean 61.8 ± 13.7%). After IVC reconstruction, the following changes were observed at anaerobic threshold: work rate increased by 14.6 W, 95%CI (-0.7; 30.0), oxygen uptake increased by 1.8 ml/kg, 95%CI (0.3; 3.3). Oxygen pulse increased by 1.95 ml per beat, 95%CI (1.12; 2.78), corresponding to a mean relative increase of 22.5%, 95%CI (12.4; 32.7) (p < 0.001). The following changes were observed at peak exercise: work rate increased by 48.1 W, 95%CI (27.8; 68.4), oxygen uptake increased by 6.4 ml/kg, 95%CI (3.8; 9.1). Oxygen pulse increased by 2.68 ml per beat, 95%CI (1.60; 3.76), corresponding to a mean relative increase of 29.4%, 95%CI (17.7; 41.2) (p < 0.001). At follow-up, 5 (29%) patients remained in NYHA class II. CONCLUSIONS In patients with chronic IVC obstruction, cardiopulmonary exercise intolerance as a result of impaired cardiac filling is at least partially reversible following endovascular IVC reconstruction. STUDY REGISTRATION URL: https://clinicaltrials.gov. Unique identifier: NCT02433054.

DOI: https://doi.org/10.1016/j.thromres.2021.03.025

Originally published at:
Sebastian, Tim; Barco, Stefano; Kreuzpointner, Robert; Konstantinides, Stavros; Kucher, Nils (2021). Reversal of cardiopulmonary exercise intolerance in patients with post-thrombotic obstruction of the inferior vena cava. Thrombosis research, 208:219-225.
DOI: https://doi.org/10.1016/j.thromres.2021.03.025

ARTICLE IN PRESS

Thrombosis Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Reversal of cardiopulmonary exercise intolerance in patients with post-thrombotic obstruction of the inferior vena cava

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ARTICLE INFO

Keywords:
Post-thrombotic syndrome
Inferior vena cava
Stent
IVC reconstruction
Cardiopulmonary exercise testing

ABSTRACT

Background: It is unclear whether cardiopulmonary exercise intolerance in patients with chronic obstruction of the inferior vena cava (IVC) is reversible following endovascular IVC reconstruction.
Methods: In 17 patients (mean age 45 ± 15 years, 71% men) with post-thrombotic syndrome due to IVC obstruction and preserved left ventricular ejection fraction (mean 58 ± 3%), we performed cardiopulmonary exercise testing before and 3 months after IVC reconstruction (mean 4.1 ± 1.5 implanted stents). The median time from latest episode of deep vein thrombosis to intervention was 150 (interquartile range 102–820) days.
Results: At baseline, 12 (71%) patients reported New York Heart Association (NYHA) class II or III symptoms, 76% did not achieve >85% of predicted oxygen uptake at peak exercise (mean 61.8 ± 13.7%). After IVC reconstruction, the following changes were observed at anaerobic threshold: work rate increased by 14.6 W, 95% CI (−0.7; 30.0), oxygen uptake increased by 1.8 ml/kg, 95%CI (0.3; 3.3). Oxygen pulse increased by 1.95 ml per beat, 95%CI (1.12; 2.78), corresponding to a mean relative increase of 22.5%, 95%CI (12.4; 32.7) ($p < 0.001$). The following changes were observed at peak exercise: work rate increased by 48.1 W, 95%CI (27.8; 68.4), oxygen uptake increased by 6.4 ml/kg, 95%CI (3.8; 9.1). Oxygen pulse increased by 2.68 ml per beat, 95%CI (1.60; 3.76), corresponding to a mean relative increase of 29.4%, 95%CI (17.7; 41.2) ($p < 0.001$). At follow-up, 5 (29%) patients remained in NYHA class II.
Conclusions: In patients with chronic IVC obstruction, cardiopulmonary exercise intolerance as a result of impaired cardiac filling is at least partially reversible following endovascular IVC reconstruction.
Study registration: URL: https://clinicaltrials.gov. Unique identifier: NCT02433054.

1. Introduction

Obstruction of the inferior vena cava (IVC) is a frequent condition and is characterized by a wide clinical spectrum, ranging from incidental diagnosis to massive bilateral iliofemoral deep vein thrombosis, chronic venous insufficiency, or post-thrombotic syndrome (PTS). The majority of symptomatic patients complain of disabling venous claudication or skin changes caused by chronic elevation of peripheral venous pressure. Some patients may experience lumbago or pelvic congestion symptoms, caused by venous hypertension in paraspinal or pelvic veins [1].

Reasons for IVC occlusion include idiopathic deep vein thrombosis, IVC filter thrombosis, inflammatory conditions (e.g. retroperitoneal fibrosis), umbilical vein catheters after early birth, or external compression syndromes (e.g. tumor, aneurysm). In addition, congenital anomalies such as IVC duplication, agenesis with azygos continuation, or atresia were occasionally described [2].

It remains hypothetical whether a chronic IVC obstruction adversely affects venous return to the heart and therefore may cause cardiopulmonary exercise intolerance [3]. In patients with IVC occlusion, limitations in exercise performance are often attributed to venous claudication or muscular deconditioning and not necessarily to impaired cardiac preload. First reports of patients with dyspnea on exertion, have been described in the context of IVC ligation [4–6]. In smaller case series, symptomatic patients with IVC ligation were characterized by limited increase in cardiac output during exercise assessed by right heart catheterization [4], and limited peak oxygen uptake during

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https://doi.org/10.1016/j.thromres.2021.03.025
Received 21 January 2021; Received in revised form 5 March 2021; Accepted 22 March 2021

cardiopulmonary exercise testing [7,8]. These observations suggest but do not prove that cardiopulmonary exercise intolerance in patients with IVC ligation may be caused by reduced venous return to the heart and its incapability to adequately increase stroke volume and cardiac output during exercise [3,4,7].

Endovascular stent reconstruction of the IVC has emerged as a potentially effective treatment for symptomatic patients with PTS, in particular in patients who are at risk to develop leg ulcers [9,10]. It is unclear whether cardiopulmonary exercise intolerance in patients with chronic obstruction of the inferior vena cava (IVC) is reversible following endovascular IVC reconstruction.

2. Methods

2.1. Patient population

Patients with chronic IVC obstruction were included in the prospective Swiss Venous stent registry from the university hospitals Zurich and Bern, an ongoing clinical study including consecutive adult patients treated with dedicated venous nitinol stents for different conditions. Main exclusion criteria for enrollment are the inability to provide informed consent, age <18 years, pregnancy or postpartum period <30 days, and an estimated life expectancy <3 month. All patients provided written informed consent to participate in the study.

Between January 2018 and May 2020, 23 patients underwent IVC reconstruction for the treatment of the PTS. For this analysis, we included consecutive patients who (1) suffered from a PTS or had venous leg claudication, (2) had post-thrombotic obstruction of the IVC, (3) had left ventricular ejection fraction >50% from a transthoracic echocardiogram within 3 months prior to intervention, (4) underwent successful endovascular stent reconstruction with patent iliofemoral and caval veins at the time of repeated cardiopulmonary exercise test, and (5) had cardiopulmonary exercise tests at baseline and 3 months after endovascular intervention. Among the 23 PTS patients with IVC reconstruction, data from 17 patients was analyzed: 4 were not included because they were unable to perform a cardiopulmonary exercise test at baseline due to severe venous claudication or physical deconditioning, 1 patient was unable to tolerate the face mask, and 1 patient had left ventricular dysfunction due to congenital heart disease.

The study was approved by the Swiss Ethics Committee on research involving humans and was not funded. The study is registered on the National Institutes of Health website (ClinicalTrials.gov; identifier NCT02433054). The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.2. Diagnosis of post-thrombotic syndrome, stent reconstruction procedure, and postinterventional anticoagulation therapy

Obstruction of the IVC and iliofemoral veins was diagnosed by Duplex ultrasound and confirmed by contrast-enhanced computed tomography or magnetic resonance venography. Patients with a Villalta score ≥5 points [11] or with symptomatic venous claudication, confirmed by treadmill exercise tests, were offered endovascular therapy. Procedural details for IVC stent reconstruction in general anaesthesia from our institution were published previously [10]. All patients were treated with anticoagulation therapy post intervention for an indefinite period of time.

2.3. Clinical follow-up and cardiopulmonary exercise testing

Routine clinical follow-up visits were performed at our outpatient clinic by vascular specialists at 3 months after the intervention. Duplex ultrasound was used for investigating stent patency prior to repeated cardiopulmonary exercise testing, based on previously published criteria [12]. Since 2018, cardiopulmonary exercise tests were routinely performed in all patients with IVC obstruction before and after IVC reconstruction in our institution. We used a research grade stationary system with standard cycle ergometer (Quark CPET®, Cosmed, Italy), as previously described [13]. Individualized ramp protocols were designed to reach the patients maximal work output between 6 and 12 min, using ramp grades between 5 and 20 W per minute at 2-min intervals. Continuous cardiopulmonary monitoring facilitated the documentation of a 12-lead electrocardiogram (ECG), cuff blood pressure, and pulse oximetry. Respiratory rate, oxygen consumption, tidal volume, carbon dioxide production, and power output were measured by a metabolic unit.

Subject effort was defined as sufficient if one of the following indicators was present at peak exercise: 1) achievement of at least 85% of predicted maximal heart rate [heart rate / (220 bmp − age) × 100]; 2) a respiratory exchange ratio (RER) ≥1.10; and 3) blood serum lactate concentration of ≥4.0 mmol/L (if available). Cardiopulmonary functional capacity was graded according to the Ludwigshafen scheme [14]: Normal cardiopulmonary capacity was defined as achievement of at least 85% of predicted oxygen uptake (VO_2) at peak exercise; in patients with <85% of predicted VO_2 uptake, the extend of impairment was graded into mild (70–84%), moderate (50–69%) and severe (<50%).

We used a 3-criteria approach to identify the anaerobic threshold: (1) identification of excess VCO_2 relative to VO_2 (V-slope), (2) identification of hyperventilation relative to oxygen, and (3) exclusion of hyperventilation relative to CO_2 at the time point identified by the previous criteria [13]. Anaerobic threshold usually occurs at 45–65% of peak VO_2 in healthy untrained subjects.

Table 1
Baseline characteristics and procedural details.

	$N = 17$
Baseline characteristics	
Age, mean ± SD	45 ± 15
Women, N (%)	5 (29)
Known thrombophilia, N (%)[a]	3 (18)
Active venous ulcers, N (%)	3 (18)
Family history of deep vein thrombosis, N (%)	3 (18)
Current smoking, N (%)	2 (12)
History of pulmonary embolism, N (%)	2 (12)
Lupus erythematodes, N (%)	1 (6)
Diabetes mellitus, N (%)	1 (6)
Coronary artery disease, N (%)	1 (6)
Inflammatory bowel disease, N (%)	1 (6)
Chronic thromboembolic pulmonary disease, N (%)	1 (6)
History of liver transplantation, N (%)	1 (6)
Baseline transthoracic echocardiography	
Left ventricular ejection fraction, %, mean ± SD (17/17)	58 ± 3
Left ventricular end-diastolic dimension, mm, mean ± SD (16/17)	48 ± 5
Tricuspid annular plane systolic excursion, mm, mean ± SD (15/17)	20 ± 5
Right ventricular fractional area change, %, mean ± SD (14/17)	38 ± 3
Right ventricular end-diastolic dimension, mm, mean ± SD (16/17)	43 ± 3
Procedural details	
Number of implanted venous stents, mean ± SD	4.1 ± 1.5
Proximal stent landing zone in suprarenal IVC/infrarenal IVC, N (%)	9 (53)/8 (47)
Distal stent landing zone in infrarenal IVC, N (%)	1 (6)
Iliac kissing stents, N (%)	15 (88)
Distal stent landing zone left side in iliac vein/common femoral vein, N (%)	11 (65)/5 (29)
Distal stent landing zone right side in iliac vein/common femoral vein, N (%)	7 (41)/8 (47)
Anticoagulation therapy: direct oral anticoagulants/vitamin K antagonists, N (%)	11 (65)/6 (35)

Data are presented as mean with ± standard deviation or numbers with percentages.

[a] Two patients had heterozygous factor V Leiden mutation, one patient had antiphospholipid antibody syndrome.

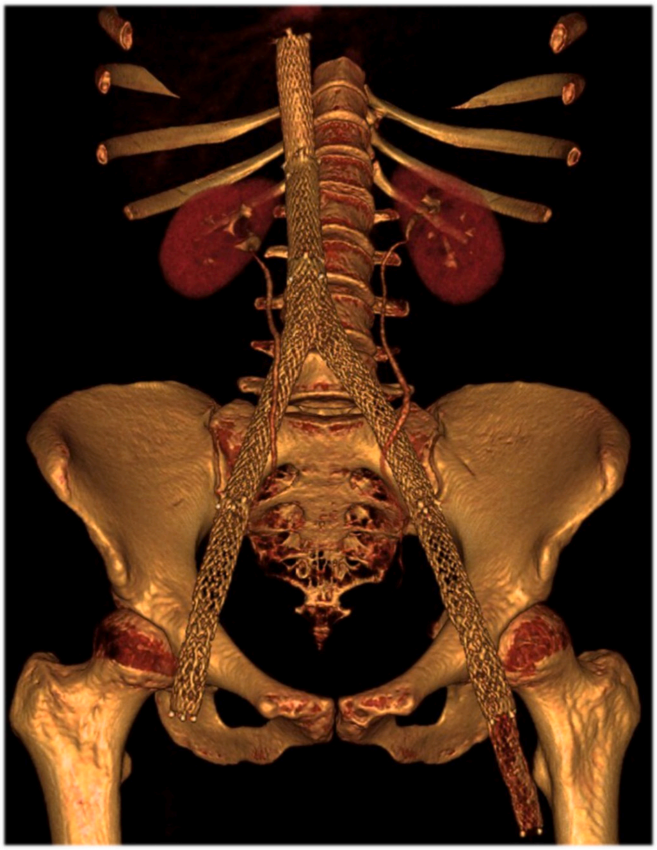

Fig. 1. Endovascular reconstruction of the inferior vena cava and iliac veins with self-expandable nitinol stents.
Three-dimensional reconstructed computed tomographic image from a patient with inferior vena cava reconstruction with self-expandable nitinol stents. The proximal stent-landing zone was in the suprarenal inferior vena cava adjacent to the right atrium. The patient received iliac kissing stents for reconstructing the ilio-caval confluence and stent extensions to both common femoral veins.

2.4. Sample size and statistical analysis

In the absence of data on change of O_2 pulse pre and post IVC reconstruction, we performed a preliminary analysis of the first 6 patients, and estimated that we would need 17 patients to demonstrate that the O_2 pulse at anaerobic threshold would increase after IVC reconstruction by 1.5 ml per heartbeat and a standard deviation 2.0, with a power 80% power to declare that the mean of the paired differences is significantly different from zero, i.e. a two-sided *p*-value is less than 0.05.

Continuous variables are accompanied by the appropriate measure of central tendency and dispersion. Categorical variables are reported as numbers and percentages. Continuous exercise variables measured pre- and post intervention were compared by paired Student *t*-test and accompanied by mean difference with 95% confidence interval (95% CI). Skewed data were compared with the Wilcoxon Rank test. A *p*-value <0.05 was considered statistically significant. Statistical analysis was performed with jamovi Version 1.2 (The jamovi project, Sydney, Australia; https://www.jamovi.org).

3. Results

The baseline characteristics of the study population are displayed in Table 1. The median time from latest episode of deep vein thrombosis to intervention was 150 (interquartile range: 102–820) days. Three patients had atresia of the IVC, most likely due to umbilical vein catheters after premature birth. Two patients had chronic IVC filter thrombosis. The filters were extracted prior to IVC reconstruction.

Table 2
Cardiopulmonary exercise testing (CPET) parameters at anaerobic threshold.

CPET parameters at anerobic threshold	Before intervention	After intervention	Mean difference (95% CI)	p-Value
Work rate, W	92.71 ± 28.83	107.35 ± 30.84	14.65 (−0.69; 29.98)	0.060
Heart rate, beats per min	128.12 ± 26.46	119.41 ± 15.57	−8.71 (−18.02; 0.60)	0.065
Respiratory rate, breaths per min	22.40 ± 4.67	21.75 ± 3.98	−0.65 (−3.22; 1.93)	0.602
Minute ventilation, l/min	36.98 ± 9.48	41.62 ± 7.45	4.64 (0.62; 8.66)	0.026
VO_2, ml/kg body weight	13.84 ± 4.71	15.64 ± 4.49	1.80 (0.32; 3.27)	0.020
- VO_2, percent of predicted	47.32 ± 13.08	54.42 ± 12.26	7.10 (2.07; 12.14)	0.009
- O_2 pulse, ml/beat	9.25 ± 2.14	11.20 ± 2.52	1.95 (1.12; 2.78)	<0.001

Data are presented as mean with ± standard deviation, and the mean difference of the paired samples was calculated with the corresponding 95% confidence interval. CI: confidence interval; CPET: cardiopulmonary exercise testing; VO_2: oxygen consumption; W: Watt.

Two patients had pre-existing cardiopulmonary conditions: one patient had mild chronic thromboembolic disease without right ventricular dysfunction or pulmonary hypertension, and one patient had stable coronary artery disease with a chronic occlusion of the left circumflex artery, preserved left ventricular ejection fraction with lateral hypokinesia. Two patients were treated with angiotensin receptor blockers for arterial hypertension, and none received beta blockers or other antiarrhythmic drugs.

Baseline echocardiography revealed preserved dimension and function of the left and right ventricles. None had direct or indirect evidence of pulmonary hypertension, including paradoxical septal motion, tricuspid regurgitation, or elevated right ventricular to right atrial pressure gradients. One patient had left ventricular hypertrophy with diastolic dysfunction.

The majority of patients had complex venous stent procedures (mean 4.1 stents), including reconstruction of the ilio-caval vein confluence with kissing stents. Almost half of the patients had overlapping stents from the inferior vena cava down to the common femoral vein (Fig. 1).

All of the 17 patients had patent venous stent implants with <50% stent stenosis at the time of repeated cardiopulmonary exercise test. Before endovascular intervention, 13 (76%) patients fulfilled at least one criteria of sufficient subject effort during cardiopulmonary exercise testing: 9 (53%) achieved ≥85% of predicted maximal heart rate, 10 (59%) showed a respiratory exchange ratio of ≥1.10, and all 7 patients with available serum lactate levels showed concentrations ≥4.0 mmol/L. After intervention, 16 (94%) patients fulfilled at least one criteria of sufficient subject effort: 13 (76%) patients achieved >85% of predicted maximal heart rate, 15 (88%) patients showed a respiratory exchange ratio of ≥1.10, and all 4 patients with available serum lactate levels showed concentrations ≥4.0 mmol/L.

3.1. Study outcomes

At baseline, 13 (76%) patients showed impaired cardiopulmonary functional capacity based on the *Ludwigshafen scale*: 3 (18%) patients had mild impairment, 10 (59%) had moderate impairment, and 4 (24%) had normal cardiopulmonary capacity. At follow-up, 9 (53%) patients showed impaired cardiopulmonary functional capacity: 7 (41%) had mild impairment, 2 (12%) had moderate impairment and 8 (47%) showed normal cardiopulmonary capacity.

Table 3
Cardiopulmonary exercise testing (CPET) parameters at peak exercise.

CPET parameters at peak exercise	Before intervention	After intervention	Mean difference (95% CI)	p-Value
Work rate, W	144.47 ± 35.01	192.59 ± 53.11	48.12 (27.82; 68.41)	<0.001
Heart rate, beats per min	156.35 ± 24.75	161.35 ± 20.15	5.0 (−2.27; 12.27)	0.164
Respiratory rate, breaths per min	29.35 ± 4.84	31.19 ± 4.22	1.84 (−0.92; 4.59)	0.177
Minute ventilation, l/min	63.64 ± 16.99	83.25 ± 20.85	19.60 (12.47; 26.73)	<0.001
Systolic BP (mmHg)	168.12 ± 29.50	174.06 ± 35.12	5.94 (−8.66; 20.55)	0.401
Diastolic BP (mmHg)	92.00 ± 16.83	90.12 ± 20.51	−1.88 (−11.74; 7.97)	0.691
VO_2, ml/kg body weight	18.03 ± 5.23	24.46 ± 8.22	6.43 (3.75; 9.12)	<0.001
- VO_2, percent of predicted	61.77 ± 13.70	83.74 ± 17.87	21.97 (14.09; 29.85)	<0.001
- O_2 pulse, ml/beat	10.03 ± 2.39	12.71 ± 2.70	2.68 (1.60; 3.76)	<0.001

Data are presented as mean with ± standard deviation, and the mean difference of the paired samples was calculated with the corresponding 95% confidence interval. BP: blood pressure; CI: confidence interval; CPET: cardiopulmonary exercise testing; VO_2: oxygen consumption; W: Watt.

None of the patients had signs of myocardial ischemia during baseline or follow-up cardiopulmonary exercise testing, including chest pain or ECG changes. Systolic blood pressure at peak exercise before and after intervention were 168 ± 30 mmHg and 174 ± 35 mmHg (mean difference: 5.9, 95%CI: −8.7 to 20.5 mmHg), respectively. Diastolic blood pressure at peak exercise before and after intervention were 92 ± 17 mmHg and 90 ± 21 mmHg (mean difference: −1.9, 95%CI: −11.7 to 8 mmHg), respectively. After IVC reconstruction, the minute ventilation (VE) at peak exercise increased from 63.6 ± 17.0 l/min to 83.2 ± 20.8 l/min (mean difference: 19.6, 95%CI: 12.5 to 26.7 l/min), and minute ventilation carbon dioxide production relationship (VE/VCO_2 slope) decreased from 30.2 ± 4.3 to 27.9 ± 4.7 (mean difference: −2.2; 95%CI 0.5 to −4.9).

Changes in work rate (WR), heart rate (HR), percent of predicted VO_2 (per kg bodyweight) and O_2 pulse (in ml per heartbeat), obtained at the time of anaerobic threshold and peak exercise are displayed in Tables 2+3 and Figs. 2+3, respectively. Mean increase in O_2 pulse at anaerobic threshold was 1.95 ml per heartbeat with a standard deviation of 1.61, which corresponds to a mean relative increase of 22.5%, 95%CI (12.4 to 32.7%; $p < 0.001$). Mean increase in O_2 pulse at peak exercise was 2.68 ml per heartbeat with a standard deviation of 2.09, which corresponds to a mean relative increase of 29.4%, 95%CI (17.7 to 41.2%; $p < 0.001$).

At baseline, 3 (18%) patients reported New York Heart Association (NYHA) class III symptoms, and 9 (53%) class II symptoms. At follow-up, no patient was in NYHA class III, and 5 (29%) patients reported class II symptoms.

In the 13 patients with sufficient subject effort, mean increase in O_2 pulse at anaerobic threshold was 1.79 ml per heartbeat with a standard deviation of 1.71, which corresponds to a mean relative increase of 22.3%, 95%CI (8.8 to 35.8%; $p = 0.003$). Mean increase in O_2 pulse at peak exercise was 2.36 ml per heartbeat with a standard deviation of 1.93, which corresponds to a mean relative increase of 27.1%, 95%CI (13.2 to 40.9%; $p < 0.001$).

4. Discussion

This is the first study of symptomatic patients with PTS or venous leg claudication associated with chronic IVC obstruction who were systematically evaluated by cardiopulmonary exercise testing before and after endovascular reconstruction. First, we found that approximately three quarter had NYHA class II or III symptoms and reduced cardiopulmonary exercise capacity before IVC reconstruction, despite the presence of preserved echocardiographic cardiac function at rest. Second, the concept of reversible cardiopulmonary exercise intolerance with IVC obstruction due to poor cardiac filling from collateral azygos and paravertebral veins confirmed for the first time, by demonstrating substantial improvement in O_2 pulse at anaerobic threshold, a surrogate of cardiac output, within a short period after endovascular IVC reconstruction. Our results show that cardiopulmonary exercise intolerance due to IVC obstruction is at least partially reversible based on a relative 22.5% increase in O_2 pulse at anaerobic threshold, observed after IVC reconstruction. The finding of improved cardiac performance paralleled a remarkable improvement in NYHA class at the time of the repeated cardiopulmonary exercise test. Minimal-invasive catheter-based techniques aiming at increasing the preload reserve may represent a curative therapy for patients with chronic IVC obstruction who experience exertional dyspnea.

In smaller case series, symptomatic patients with IVC ligation were characterized by limited increase in cardiac output during peak exercise by right heart catheterization [4], and limited peak oxygen uptake during cardiopulmonary exercise testing [7,8]. Measurements at anaerobic threshold may better reflect changes in cardiac hemodynamics in patients with initially low exercise capacity who may experience an improvement in PTS severity following endovascular intervention for two reasons: (1) many PTS patients do not fulfill the criteria of sufficient subject effort during cardiopulmonary exercise testing as confirmed by our study, (2) recanalization of the IVC is associated with improvement in PTS severity and venous claudication [10,15,16], and therefore may potentially improve peak exercise performance and VO_2 independent from cardiac effects. Of note, we also observed a trend towards lower heart rate at anaerobic threshold after IVC reconstruction, which is not explainable by a reduction in exercise-induced venous claudication.

To date, the indication for endovascular IVC reconstruction is the presence of the PTS, and the presence of cardiopulmonary exercise intolerance is not yet considered an indication for revascularization. In a recent study of patients with IVC stents, primary and secondary patency rates with new-generation nitinol stents at 2 years were 57% and 87%, respectively [10]. Stent thrombosis occasionally occurs despite anticoagulation therapy, particularly in patients with post-thrombotic femoral veins. Nevertheless, there was remarkable improvement in PTS severity (Villalta score) and ulcer healing after endovascular IVC reconstruction in several studies [10,15,16].

Our study has limitations. First, the sample size was small and patients were followed only for 3 months after endovascular therapy. The benefit observed in cardiac hemodynamics and NYHA class remains to be confirmed in the long term: we speculate, however, that the benefit would persist as long as IVC stents remain patent. Second, we used noninvasive gas exchange parameters to assess cardiac function: right heart catheterization during exercise would have been helpful to directly assess cardiac output and pressures before and after IVC reconstruction. Third, 4 of the 17 patients had insufficient subject effort at the baseline cardiopulmonary exercise test which could have affected the results of our study. When analyzing the 13 patients with sufficient subject effort separately, however, we found a similar and significant increase in O_2 pulse at anaerobic threshold and peak exercise. Fourth, limitations of the pre-post study design are well known and primarily regard the causal effect attributed to the intervention, including unexpected temporal changes, regression to the mean, testing threat, and non-specific effects of the intervention on the outcome. In this group of patients with

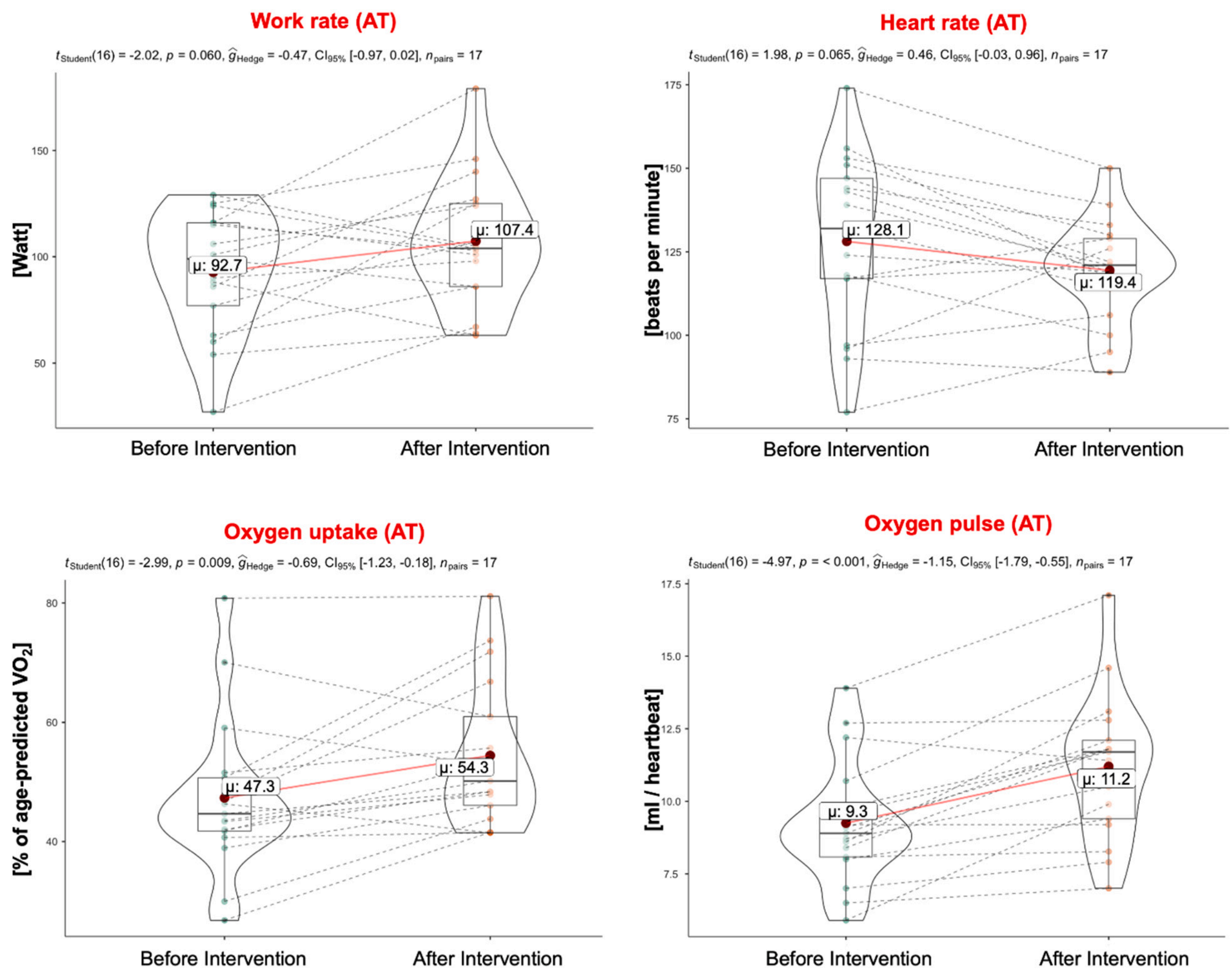

Fig. 2. Changes in work rate, heart rate, oxygen uptake and oxygen pulse at anaerobic threshold (AT) before and after stent reconstruction of the inferior vena cava. Grouped box plots with density curves (Violin plots) display changes in work rate (top left), heart rate (top right), predicted oxygen consumption (bottom left) and oxygen pulse (bottom right) at the time of peak exercise. Values derived from cardiopulmonary exercise tests, and were obtained before and after endovascular reconstruction of the inferior vena cava. The box plots depict the 95% confidence intervals with mean (μ) and median (horizontal line), while the width of each curves corresponds to the frequency of each data point (density).

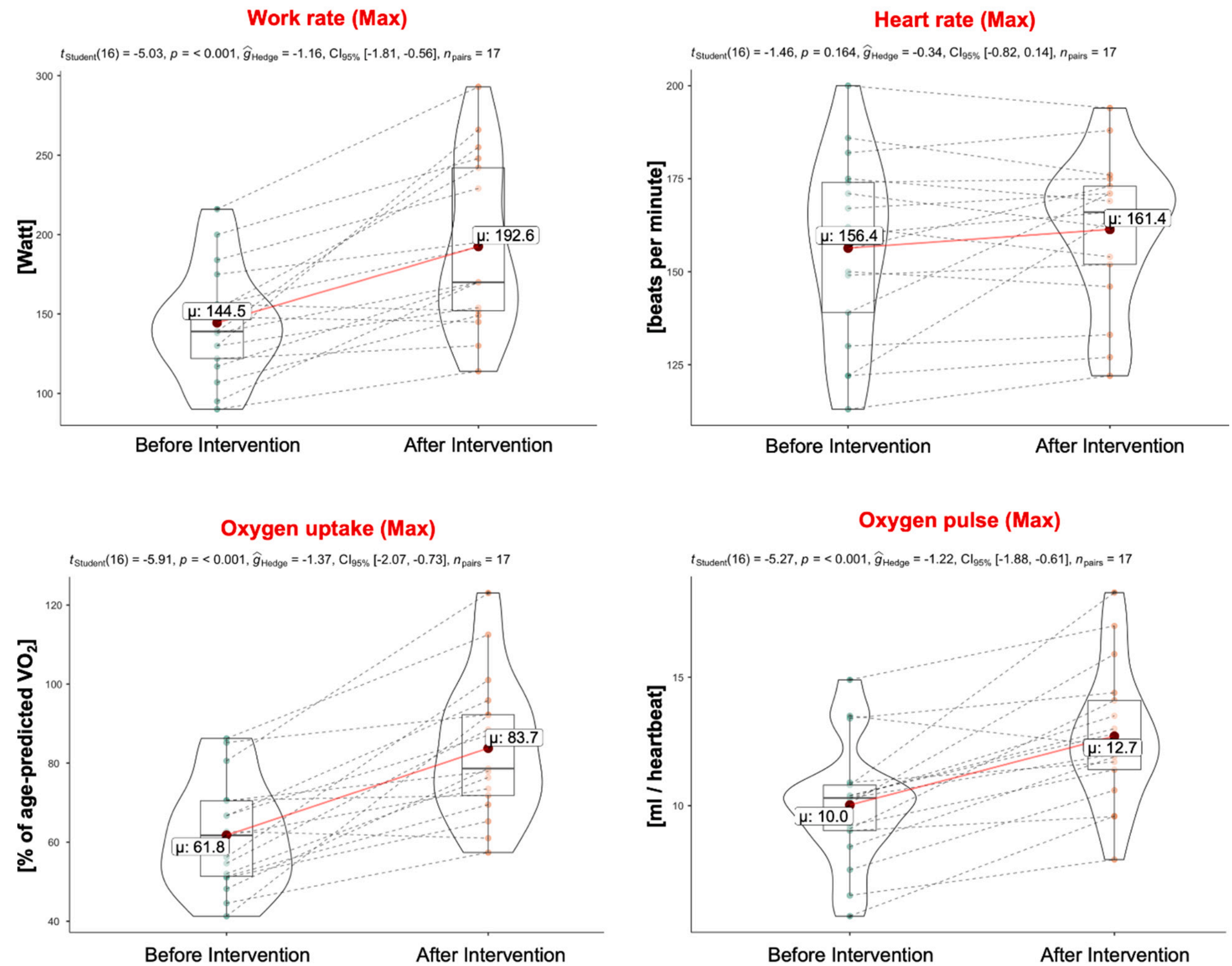

Fig. 3. Changes in work rate, heart rate, oxygen uptake and oxygen pulse at peak exercise (max) before and after stent reconstruction of the inferior vena cava. Grouped box plots with density curves (Violin plots) display changes in work rate (top left), heart rate (top right), predicted oxygen consumption (bottom left) and oxygen pulse (bottom right) at the time of peak exercise. Values derived from cardiopulmonary exercise tests, and were obtained before and after endovascular reconstruction of the inferior vena cava. The box plots depict the 95% confidence intervals with mean (μ) and median (horizontal line), while the width of each curves corresponds to the frequency of each data point (density).

symptomatic PTS and chronic IVC obstruction, we interpreted the changes in cardiopulmonary exercise parameters hypothesizing a zero-effect.

In conclusion, we describe a novel form of cardiopulmonary exercise intolerance secondary to impaired cardiac filling from chronic IVC obstruction. Our results indicate that endovascular IVC reconstruction has the potential to improve cardiopulmonary exercise intolerance in patients with chronic IVC obstruction.

Source of funding

None.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: TS, SB, RK and SK have no relationships relevant to the context of this paper to report. NK reports personal fees from Boston scientific, Optimed, Bard, BTG, and plusmedica.

Acknowledgement

We are pleased to acknowledge the work and contribution of Dr. Rebecca Spescha, Dr. Claudia Leeger, Stephanie Roth and Eliane Probst to the Swiss Venous Stent Registry.

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